

ASCCP Risk-Based Management Consensus Guidelines: New Recommendations for Public Comment

Introduction: The ASCCP Risk-Based Management Consensus process to revise the 2012 guidelines for management of abnormal cancer screening began in February 2018 and will culminate with public release of guidelines, currently planned for 2020. This process involves experts in cervical cancer prevention, [representing nearly 20 organizations](#), including, for the first time, patient advocacy groups. Organization representatives have been meeting in working groups to create evidence-based, precise recommendations for care.

This document, *ASCCP Risk-Based Management Consensus Guidelines: New Recommendations for Public Comment*, is the first public release of the principles underlying these guidelines. It describes substantive changes to the 2012 guidelines. Two companion documents are also available for comment:

- [Recommendations from the 2012 guidelines recommended for continued use in the new risk-based guidelines](#) includes 2012 guidelines that will continue for clinical management in the new risk-based guidelines.
- [Data and References](#) describes the data sources in detail and includes selected references from the published literature that inform guidelines development.

Public Comment Period on Preliminary Guideline Language

The preliminary language for the new risk-based consensus guidelines is being made available for [comment](#). We do not consider these guidelines to be “DRAFT,” in the sense we are looking for agreement or disagreement with the specific statements. Instead, we are calling them “PRELIMINARY,” because the final language will be shaped by the public comments we receive, as well as additional data review and feedback from representatives of national organizations during the planned consensus conference in October 2019. Although open to the public for comment, these guidelines are intended for use by healthcare providers and may contain vocabulary that is not familiar to the lay public. A [glossary](#) has been developed to define certain medical terms (located at the end of this document).

Comments are welcome on any portion of this document. The material is presented below in the following categories:

- Summary of New Guidelines: Evolution from 2012 Guidelines
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- New Guidelines for Public Comment
 - [Section 1: Clinical Action Thresholds](#)
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Summary of New Guidelines: Evolution from 2012 Guidelines

Rather than consider results from screening and management tests in isolation, the new guidelines use current and past results to achieve a more precise assessment of risk for cervical precancer. The goals are to increase accuracy and reduce complexity for providers and patients. Cervical precancer is the target of screening, which we detect and treat to prevent cancer. The goals are to increase accuracy of risk estimates for precancer and, at the same time, to reduce complexity of clinical management for providers and patients.

Individual risk estimates are called risk levels. Risk levels will lead to one of three management options: **surveillance, colposcopy, or treatment**. Clinical Action Thresholds, chosen by consensus of the guidelines group, define risk bands or ranges judged to mandate the different management options. The combination of a patient's risk level, determined by prior history and current results, and the consensus Clinical Action Thresholds, will assign for each patient a personalized risk score and a simple recommendation for management (summarized in Figure 1 and defined in detail below).

Figure 1. Summary of Risk-based Clinical Action Thresholds

	Surveillance		Colposcopy		Treatment	
CIN3+ risk	Return in 5 years equivalent to general population with one negative HPV or co-test	Return in 3 years similar to a negative screening cervical cytology	Return in 1 year between colposcopy and 3-year return thresholds	Colposcopy Approximate risk of low-grade to moderately abnormal results in a screening population (e.g. LSIL)	Colposcopy or Treatment Approximate risk of moderate to high risk results in a screening population (e.g. ASC-H)	Treatment preferred* Very high risk results (e.g. HSIL/HPV 16+) <i>*treatment without biopsy, see-and-treat</i>
	≤0.1% at 5 years	0.2% -0.5% at 5 years	0.6% at 5 years to <4% immediate risk	4%-24% immediate	25%-49% immediate	≥50% immediate

***Note that the risk levels that prompt different management options have been similar through the 2006, 2012, and new risk-based management guidelines.*

Guideline Revision Process

The guideline revision process involves seven working groups to produce the following components:

- Clinical Action Thresholds
 1. Surveillance
 2. Colposcopy
 3. Treatment
- Clinical factors to include in risk assessment, and guidelines for special populations, including pregnant individuals and immunocompromised patients
 4. Risk Modification
- Modeling to provide information on costs and long-term outcomes not available in existing data sets or literature
 5. High Value Care

Two additional working groups are contributing to the new risk-based consensus guidelines process and will continue beyond their release to help ensure that all patients receive the most appropriate level of care in a timely fashion. Guideline updates will continue to evolve along with emerging science in cervical cancer prevention.

6. Communications: spearheads the dissemination of guidelines to professional organizations and the lay public.

7. **New Technology:** develops criteria that can be used presently and, in the future, to assess technologies that are involved with the management of abnormal screening test results. Provides guidance on evaluation of new technologies. Also stresses specific recommendations of LAST and WHO terminology for reporting cervical histopathology results (Section 3).

Because the new risk-based guidelines will be electronic, (i.e. used via technology such as a smartphone application or website), they will incorporate new technologies as sufficient supportive evidence becomes available. The ability to adjust to the rapidly emerging science faster than revision of guidelines every 5-10 years is critical for the long-term utility of the guidelines.

New Foundational Principles for new risk-based guidelines

[Several foundational principles are retained from 2012](#), including equal management of equal risks, and the need to balance benefits and harms. Foundational principles that are new for these guidelines include:

- **Cancer prevention through detection and treatment of cervical precancer is the primary goal of management.** Different definitions and nomenclatures for cervical lesions and precancers exist. The LAST (lower anogenital squamous terminology) Project and the WHO recommend a 2-tiered terminology (LSIL/HSIL) for reporting histopathology of HPV-associated squamous lesions, similar to the Bethesda system used for reporting cervical cytology. Historically, however, the 3-tiered CIN terminology has been used and the majority of high-level data used to generate management guideline recommendations are based on the CIN terminology.

For the management guidelines, we are using CIN3 as the best surrogate of precancer. CIN3+ (which includes CIN3, AIS, and cervical cancer) is chosen instead of CIN2+ because it is a more pathologically reproducible diagnosis. CIN3+ is chosen instead of cancer alone because cancers are rare and often occur in unscreened individuals; therefore, the available data from screened populations are sparse and do not provide stable risk estimates. These management guidelines consider CIN3+ risk at the time point relevant for the clinical action being

considered—Clinical Action Thresholds for colposcopy and treatment use immediate risks of CIN3+, while longer term surveillance recommendations use 5-year risks.

- **Optimal risk estimation incorporates current results and past history.** Previous guidelines recommended management based on current, individual test results. The new guidelines are based on the principle that persistent HPV infection is necessary for developing precancer (CIN3+), and the duration of the persistent HPV infection is a critical factor in estimating precancer risk. HPV type, when available, is also important for risk stratification.

Therefore, prior HPV test results and/or history of precancer (defined as histologic HSIL or CIN2/3) are the most important risk stratifiers. Prior normal cytology results are not sufficient for risk stratification. New data demonstrate that a negative HPV test immediately preceding a low-grade abnormal co-test result reduces the estimated risk of CIN3+ of that result by approximately 50%, compared to an unknown history or prior HPV+ result. Incorporating this knowledge will allow more aggressive management for individuals with persistent infections, who are at higher risk for CIN3+, while avoiding unnecessary interventions for individuals with new or latent HPV infections who are at lower risk.

As a result, in these guidelines, management can differ for the same current test result depending on the result from preceding tests

- **Multiple datasets will be used to calculate risks.** Prior guidelines relied heavily on a large prospective dataset from Kaiser Permanente Northern California (KPNC). To ensure that the new guidelines are relevant and applicable to the entire US population, data from multiple sources are being analyzed, including screening and followup data from a national program that serves low-income and minority women.
- **Hierarchy of data.** To determine the best management strategies, large prospective, longitudinal databases are used whenever possible. Literature review is used to address questions that cannot be answered by primary data. For areas where neither primary data nor literature provide sufficient evidence, previous guidelines or consensus opinion are used.

Section 1: Clinical Action Thresholds

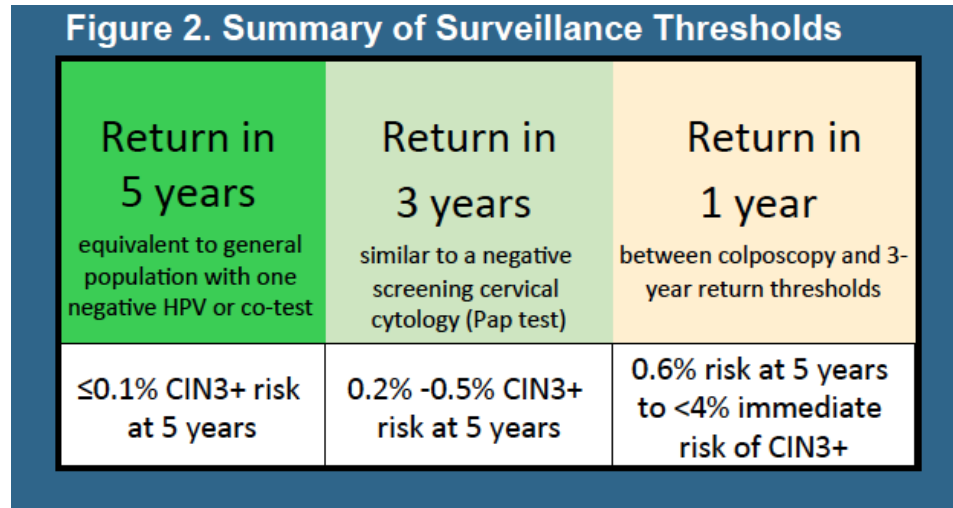
Surveillance

Introduction:

Surveillance is defined as testing at a shorter interval than that recommended for routine screening.

Surveillance is recommended for patients whose

risk of CIN3+ based on screening results and history is higher than the risk for the general screening population, but lower than those for whom colposcopy would be recommended.



Unlike colposcopy and treatment, which are performed as soon as possible after a qualifying abnormal result, surveillance involves intervals from 1-5 years. Therefore, rather than consider the immediate risk of CIN3+, we considered the 5-year risk of CIN3+ when choosing our thresholds.

The proposed surveillance intervals are defined in Figure 2, and explained in detail below. Note that most of these thresholds are based on the principle of equal management for equal risks, and are therefore similar to those outlined in 2012 guidelines.

- A 5-year return threshold approximates the risk following a negative HPV test or cotest in the general population: defined as 0.1%.¹
- 3-year return is recommended when risks fall below the 3-year return threshold and above the 5-year return threshold. A 3-year return threshold approximates the risk following a negative cervical cytology screen in the general population: defined as 0.5% CIN3+ risk at 5 years.

¹ Risk estimations up to 0.14% will be rounded down and considered as 0.1% for the purpose of risk estimation

- 1-year follow-up is recommended when CIN3+ risks are below the colposcopy threshold and above the threshold for a 3-year return. The colposcopy threshold is defined above.

Surveillance Clinical Action Thresholds

1. When patients have an estimated 5-year CIN3+ risk of $\leq 0.1\%$ based on prior history and current results, return to routine screening at 5-year intervals is **recommended**.

Rationale: Employing the principle of equal management for equal risks, this risk corresponds to the 5-year CIN3+ risk following negative HPV-based screening (primary HPV screening or cotesting) in the general population.

Low grade cytologic or histologic abnormalities are thought to indicate transient HPV infection, not precancer. Therefore a negative HPV test following low grade abnormalities is thought to indicate resolution. The estimated 5-year CIN3+ risk for an individual with a low grade abnormality followed by two negative HPV-based tests is 0.2%. This estimated risk is slightly higher than the general population risk following a negative HPV test or cotest, which is a 0.1%. A third negative HPV test or cotest appears to decrease the CIN3+ risk to $\leq 0.1\%$ at 5 years, but the estimates are less certain because fewer patients have this length of follow-up. If we recommend return to 5-year intervals after three negative HPV-based tests, most patients with low grade abnormalities will return to 5-year screening. If we do not, patients would continue to return at three years following all abnormal results, until additional data accrue.

**Note this applies only to low-grade abnormalities; high-grade abnormalities are addressed below*

Please go to the [survey](#) to give your opinion on the following question: For patients initially diagnosed with low grade cytologic or histologic abnormalities or HPV infections, that have had three negative consecutive HPV-based tests: should the new guidelines recommend returning patients to routine screening at 5-year intervals?

2) When patients have an estimated 5-year CIN3+ risk above 0.1% but below 0.5% based on prior history and current results, repeat testing in three years with HPV-based testing is **recommended**.

Rationale: Employing the principle of equal management for equal risks, this risk corresponds to the 5-year CIN3+ risk following negative cervical cytology (Pap testing).

Implications: Three-year surveillance is recommended for individuals whose risk falls between three-year follow-up and return to routine screening. Consistent with 2012 guidelines, the majority of low-grade results reach the threshold for 3-year surveillance after a single negative HPV-based test (e.g. LSIL/HPV+ → colposcopy shows CIN1 → follow-up HPV or cotest is negative → next testing recommended at three years). Also consistent with previous guidelines, ASCUS/HPV- can return at three years.

3) For patients whose estimated risk of CIN3+ risk based on prior history and current results is below the threshold for immediate colposcopy (4% immediate risk) and above the 3-year follow-up threshold (0.5% at 5 years), repeat testing in one year with HPV-based testing is **recommended**.

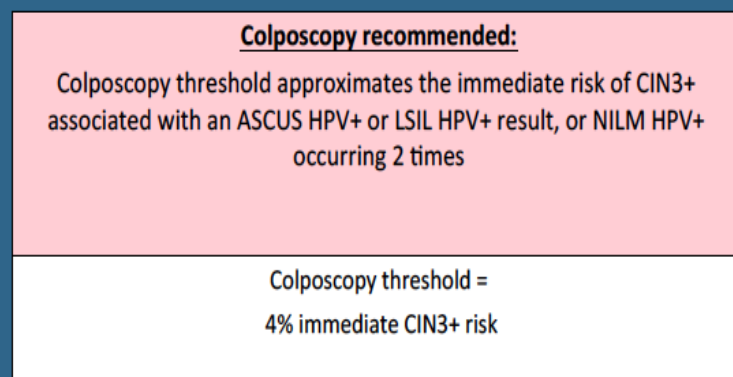
Rationale: One-year surveillance implies close follow-up for those whose risks fall between immediate colposcopy and extended interval follow-up.

Implications: Consistent with 2012 recommendations, follow-up at one year will be recommended following screening tests showing HPV+/NILM or HPV-/LSIL, colposcopic biopsies diagnosed as <HSIL/CIN2. New for these guidelines is the documented, substantially reduced CIN3+ risk following a negative HPV test or negative colposcopic examination. Based on lower CIN3+ risks, 1-year surveillance, not colposcopy, will be recommended for most cases of HPV+ ASCUS or LSIL results following a documented negative HPV test, negative cotest, or negative colposcopic examination.

Colposcopy

Introduction: Colposcopy remains a critical part of U.S. cervical cancer screening practice. Screening identifies a group of individuals at risk for precancerous lesions, who then undergo colposcopy to detect cancer precursor lesions by histopathologic diagnosis of colposcopically-directed biopsies. Colposcopy serves as the intermediate step between screening and treatment of precancerous lesions.

Figure 3. Summary of Colposcopy Threshold



While the current 2012 management guidelines for colposcopic referral were based on the projected 5-year risks of CIN3+ (including CIN3, AIS, and cancer), the new consensus management recommendations concentrate on the immediate risks of diagnosing CIN3+ at colposcopy. The practice of colposcopy has also been more precisely defined through the recently endorsed [ASCCP Colposcopy Standards](#). The recommended risk-based approach to colposcopy, including multiple biopsies of each acetowhite area, leads to more sensitive detection of CIN3+.

Under the principle of “equal management for equal risk,” the same clinical action threshold for referral to colposcopy was chosen for both initial referral due to abnormal screening results and repeat referral among individuals undergoing surveillance testing after initial colposcopy.

Colposcopy Clinical Action Threshold

When individuals have an estimated immediate risk of diagnosis of CIN3+ of 4.0% or greater based on prior history and current results, referral to colposcopy is **recommended**.

Rationale: This clinical action threshold retains the current standard of cancer prevention through detection of CIN3+, while the refined risk assessment reduces the number of colposcopies where detection of CIN3+ is unlikely. In populations undergoing HPV-based screening (cotesting or primary HPV testing) for the first time, approximately 4-5% of screening results would be referred for colposcopy, and histologic HSIL(CIN2+) would be

found in 20% of referrals. This is consistent with the current referral standard (2012 guidelines). Using the 4.0% threshold, ASCUS HPV+/LSIL would be referred immediately for colposcopy, and HPV+ /NILM would undergo surveillance in one year with repeat HPV-based testing.

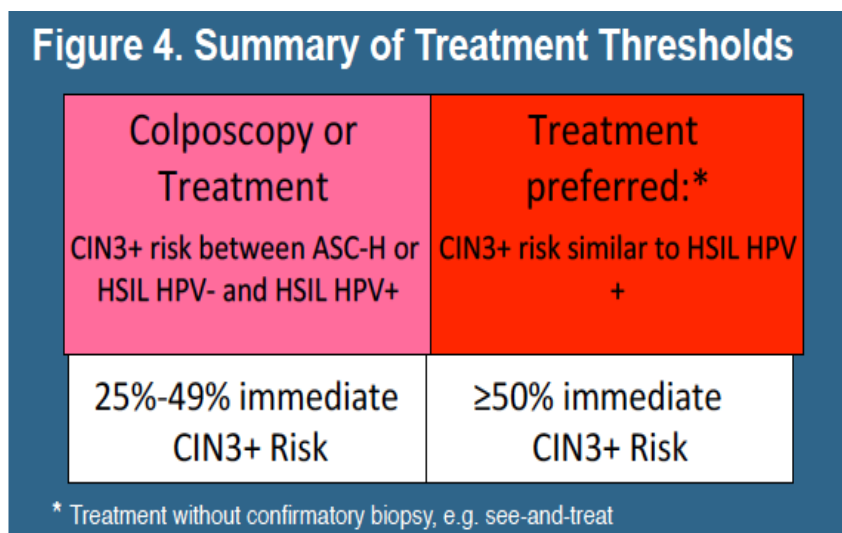
Impact over time in a population with HPV-based screening: The choice of 4.0% immediate risk of CIN3+ as the colposcopy referral threshold for colposcopy will likely lead to a reduction in unnecessary colposcopy procedures starting with the second screening round using HPV-based testing. In the general U.S. population, more than 90% of screened individuals aged 30-65 have a negative HPV test. Following a negative test, new abnormal results found at the next screening round mainly represent new HPV infections. New HPV infections are low-risk, regardless of patient age.

For example, following a negative first HPV test, a next-round result of HPV+ ASC-US or LSIL would have an immediate CIN3+ risk substantially below the colposcopy threshold, leading to a clinical action of surveillance instead of colposcopy. The choice of a threshold of 4.0% immediate risk of CIN3+ in the new risk-based guidelines produces the same rate of colposcopic referral when compared with 2012 guidelines at the first round of HPV-based screening, with a large drop anticipated in subsequent referrals.

Treatment

Introduction: The goal of treatment is cancer prevention through destruction of precancerous cells (CIN3+) prior to possible invasion. The immediate risk of CIN3+ is used to make clinical decision for treatment. The immediate risk was chosen because in the KPNC data,

the immediate, 3-year, and 5-year risks of CIN3+ are very similar for many histologic and HPV



combinations due to very high rates of treatment in that population. Therefore, use of the immediate risk of CIN3+ is most logical. In the absence of therapy, up to 30% of CIN3 will progress to invasive cancer. To avoid progression to cancer, CIN3 should be treated in virtually all circumstances, except pregnancy.

In contrast to CIN3, CIN2 has at least a 30% risk of persisting or progressing to CIN3.

Therefore, **consistent with prior guidelines, the threshold for treatment remains HSIL (by LAST terminology) or CIN2+ (by 3-tiered terminology) except in special circumstances (see below).** Treatment of high-grade CIN (HSIL or CIN2/CIN3) effectively prevents progression to invasive cancer. Historically, this recommendation has been successful because following treatment, approximately 40-95% of HPV infections clear within one year, and 90-95% of high-grade CIN resolves.

When pathologic analysis specifies that a lesion is CIN2, observation may be considered in women desiring future reproductive potential. A substantial proportion of CIN2 resolves without treatment, ranging from 20% clearance in one investigation to over 70% regression to CIN1 or normal in another. Therefore, treatment decisions for CIN2 depend on specific patient factors, including the individual's likelihood of HPV clearance and the desire for future reproductive potential. Unlike CIN2 and CIN3 (histologic HSIL), CIN1 (histologic LSIL) is considered a histologic proxy for active HPV infection, not a true precancer. Therefore CIN1 can be observed because the risk of progression to a high-grade lesion and cancer is very low. Treatment of CIN1 may be considered when it persists for two years or more; treating CIN1 increases the chance of HPV clearance.

Prevention and diagnosis of cervical cancer should remain the primary objective of cervical cancer screening and management of abnormal testing in all patients, including those of reproductive age. The effect of treatment on future pregnancy is uncertain and differentiating the increased baseline risk of preterm delivery due to the presence of histologic HSIL(CIN2/3) from an increased risk due to treatment is very challenging and existing data are conflicting.

Treatment of patients with a desire for future reproductive potential should always be guided by the most up-to-date consensus guidelines.

Treatment Clinical Action Thresholds

1. For patients with an estimated immediate risk of CIN3+ of greater than or equal to 50% based on prior history and current results, treatment using an excisional procedure without prior biopsy confirmation (see-and-treat) is **preferred**. Treatment after colposcopy and biopsy confirmation of HSIL(CIN2+) is **acceptable**.

Rationale: Treatment without biopsy confirmation has historically been an acceptable therapy for cytologic HSIL due to the substantially elevated risk of CIN3+. In the present guidelines, the immediate CIN3+ risk of an HSIL cytology was used to set as the threshold for immediate treatment without biopsy confirmation. Both retrospective and prospective studies have shown that treatment without prior biopsy resulted in a diagnosis of CIN3+ in 49% to 75% of specimens. KPNC data demonstrate that patients with an HSIL cytology and HPV+ test combination have an immediate risk of CIN3+ of 48.5% which equates to a 77% immediate risk of CIN2+. Cytologic HSIL with another risk factor, such as HPV16+ or unknown screening history, have immediate CIN3+ risks that exceed 60%. Based on the KPNC data setting this threshold would result in 2.1 Loop Electrosurgical Excision Procedures (LEEPs) to treat one person with CIN3+.

2. For patients with an estimated immediate risk of CIN3+ greater than or equal to 25% based on prior history and current results, treatment using an excisional procedure without prior biopsy confirmation (see-and-treat) or treatment after colposcopy and biopsy confirmation of histologic HSIL(CIN2+) are both **acceptable**.

Rationale: The present guidelines for treatment without biopsy proven histologic confirmation include patients who have HSIL cytology independent of HPV status. While they make up a small percentage of individuals with HSIL, in the KPNC data set, this population of patients has an immediate risk of CIN3+ of 25%, and an immediate risk of histologic CIN2+ of 47%. Based on the KPNC data setting this threshold would result in 2.8 LEEP's to treat one person with CIN3+.

Implications of treatment thresholds: Treatment without biopsy confirmation is acceptable for all high grade cotest results, such as HPV+ ASC-H and HSIL. Treatment without biopsy confirmation is preferred for individuals with HSIL and one other risk factor, such as HSIL/HPV16+.

Section 2: Risk factors and special populations

Introduction: This guideline will take into account prior risk factors that might influence risk thresholds. The group considered factors that might influence risk estimates to determine their importance for inclusion in clinical applications of the guidelines, taking into account both the magnitude of effect on the estimated risk, as well as the feasibility of collecting accurate data in clinical practice. This will assist providers in individualizing management. Factors of clear importance, such as current HPV test and cytology results, prior HPV test results, and prior history of histologic HSIL (CIN2/3), are discussed in Sections 1 and 4. Additional factors and special populations discussed below include pregnancy, immunosuppression, HPV vaccination history, hormonal contraception, history of sexually transmitted infection, multiparity, cigarette smoking, obesity, and sexual behaviors including age of first intercourse and multiple partners.

Pregnancy

Management guidelines for pregnant individuals were considered, and literature published since 2012 was reviewed. However, data in pregnancy are limited, and given the unique implications for the mother and the pregnancy shared clinical decision-making is critical for management decisions.

Pregnancy does not appear to alter the risk for or rate of progression from cervical pre-cancer to cancer, and colposcopy-directed biopsies in pregnant patients appears safe. Based on the new threshold criteria, among well-screened populations, fewer individuals will be referred to colposcopy and those referred will be at higher risk of immediate CIN3+ due to persistent HPV infections or prior HSIL (CIN2/3). Therefore, in pregnancy, management of abnormal screening results using the same risk thresholds established for non-pregnant individuals is **recommended**. Management should include limiting the number of biopsies.² Endocervical curettage and endometrial biopsy are **unacceptable** in pregnancy. If a patient has a suspected cancer by cytology or colposcopic impression, adequate biopsies to obtain sufficient tissue are **recommended**. Treatment is **not recommended** unless cancer is pathologically confirmed.

² Since bleeding is commonly associated with biopsies in pregnancy, limiting the number of biopsies should be considered, specifically if the referral was for less than HSIL and the colposcopic impression is low grade.

If treatment is deferred for a pregnant patient who otherwise would have been treated (e.g. HSIL/CIN2/3/AIS), surveillance colposcopy and testing (diagnostic cytology/HPV) in pregnancy is recommended every 12-20 weeks with intent for treatment postpartum. Repeat biopsy is only recommended if the appearance of the lesion or the cytology worsens. In the postpartum period, the treatment procedure or a full diagnostic evaluation (cervical cytology, HPV, colposcopy and biopsy) is recommended no later than 16 weeks but no earlier than four weeks postpartum.

Immunosuppression

Data reviewed generally indicated similar CIN3+ risks following abnormal results in immunocompetent and immunocompromised individuals; the preponderance of data were in HIV+ individuals. Therefore, for immunocompromised individuals, management of abnormal screening results using the same risk thresholds established for the general screening population is **recommended** except for those less than 25 years of age. Immediate referral to colposcopy is recommended for all abnormal results, including ASCUS HPV- and LSIL HPV-, even in those under 25 years of age. Existing CDC guidelines (aidsinfo.nih.gov) should be followed for screening, which includes screening within one year of sexual debut.

Summary of risk factors NOT included in risk estimates: Factors reviewed were selected by literature review and expert opinion. The goal was to determine a) the extent to which calculated CIN3+ risk would be modified, and b) the extent to which these factors could be reliably and easily determined in clinical practice.

The following factors were excluded because they did not measurably affect risk in the Kaiser Permanente Northern California (KPNC) data analysis, or the risk modification could not be sufficiently estimated:

HPV vaccination. Several studies indicate a reduced risk of CIN3+ in vaccinated individuals. However, the decision was made to exclude HPV vaccination from management recommendations at this time for three primary reasons. First, vaccine effectiveness may vary by age at series initiation and number of doses received. As obtaining accurate historical information about vaccine receipt, age, and number of doses is difficult, there is a substantial possibility for harm due to inadvertently managing an unvaccinated individual as vaccinated. This is especially important as the majority of

individuals currently 21-24 years old were not fully vaccinated early enough for maximum benefit. The second reason is data from KPNC showing that CIN3+ risks associated with LSIL and HSIL results in 21-24 year olds did not change over time. This indicates that, among individuals with abnormal results, the majority are either unvaccinated or ineffectively vaccinated. Therefore different management is not warranted. Finally, guidelines governing management of patients age <25 years are quite conservative, recommending colposcopy only after an HSIL result or three consecutive ASCUS or LSIL results, therefore applying them to vaccinated individuals has a low risk of harm.

Hormonal contraception. Limited data were available in the KPNC data analysis for CIN3+ risk. Overall, relatively short duration of use was reported in the majority of the population, and no increased risk was demonstrated. Increased cervical cancer risk has been observed in individuals using 10 years or more of combined oral contraceptive use. The literature suggests that once HPV persistence is controlled for in analysis, the hormonal effect is negligible. Whether hormones affect HPV persistence is conflicting in the literature.

History of sexually transmitted infection. The KNPC data did not show an increase in risk of CIN3+ associated with a sexually transmitted infection, after controlling for HPV infection. KPNC is a relatively low risk population, consequently it remains unclear if there is an increased risk in certain populations. However, in populations that have high rates of sexually transmitted infections, HPV is also a common co-infection confounding most analyses. There is conflicting evidence regarding chlamydia's role in cancer development and HPV persistence. In addition, the reliability of patient-reported sexually transmitted infection history is poor making this variable difficult to assess accurately.

Multiparity. Studies have shown that multiparity (>4 live births) is associated with increased cancer risk. Most studies have not controlled for partner sexual behavior making any conclusions difficult. Analysis of KPNC data showed no association, but the group of women with >4 live births was small.

Cigarette smoking. The majority of studies demonstrate an association with cigarette smoking, HPV persistence, and cancer development. However, the relative risk of

smoking after controlling for HPV infection is small with minimal impact on absolute risk. Thus, the data do not support risk modification (i.e. lowering risk threshold for triage or treatment). Yet, given the myriad of negative health effects caused by smoking, it is recommended that cessation counseling should be provided as part of evidence-based clinical care.

Obesity (elevated Body Mass Index) There is strong evidence from KPNC that detection of cervical precancer is reduced in obese women compared to normal weight women, and that risk of cancer is increased in obese women, likely due to missed detection of precancers. It is important to ensure adequate sampling and cervical visualization in obese women. However, due to its complex relationship with precancer (reduced detection) and cancer (increased risk), BMI is not included in precancer risk estimation at this time.

The following factors were excluded due to clinical impracticality of obtaining accurate, reliable information as well as conflicting data: sexual history, including age at first intercourse and number of sexual partners.

Section 3: New Technologies and Statement Regarding Lower Anogenital Squamous Terminology (LAST)

Introduction: The new technologies working group has an ongoing mission that will continue beyond the release of the new risk-based guidelines. The objective of the New Technology group is to evaluate existing and future technologies that apply to the management of abnormal screening tests. The group is tasked with developing criteria that can be used presently and, in the future, to assess technologies that have the potential for use in the management of abnormal screening test results. As the group assesses any new technology, it will make recommendations as to when such technology should be incorporated into the risk estimations.

In addition, this group may evaluate existing terminology or classification systems to ensure effective use of new or existing technologies. The first statement from this group pertains to the LAST terminology. Emerging data indicate that individuals desiring future reproductive potential may benefit from conservative management of CIN2 with observation up through age 39. A two-

tiered histologic classification would not allow for this management possibility. Therefore, proposed revisions strongly recommend qualifying an HSIL histologic diagnosis as CIN2 or CIN3.

LAST Statement Update: Proposed ASCCP Risk-Based Management Consensus Guidelines statement on the use of a two-tier terminology (LSIL/HSIL) for reporting histopathology of squamous lesions of the anogenital tract.

1. It is important to use p16 immunohistochemical (IHC) staining according to the guidance provided by the CAP-ASCCP LAST Project. p16 IHC should be used for specific indications as recommended by LAST when interpreting the H&E slide. **A positive p16 immunostain supports the diagnosis of HSIL if the morphological assessment of H&E slides is consistent with CIN2 or CIN3.** There is a risk of overcalling cervical histology results when p16 is used incorrectly. **Most importantly, a morphologic CIN1 on H&E should not be upgraded to HSIL(CIN2) even if p16 positive.**
2. For epidemiologic and clinical management purposes, **it is strongly recommended to qualify an HSIL result by –CIN2 or –CIN3, according to the options given by the LAST guidelines.** This qualification can have clinical importance, e.g. when deciding about conservative management of CIN2. It is also important for post-vaccine surveillance studies and quality control assessments of cervical precancer that have relied on CIN2 and CIN3 endpoints. Further, it is important for future research efforts to qualify HSIL –CIN2/ -CIN3 to make endpoints compatible with the histologic endpoints used for current guidelines.

Section 4: HSIL(CIN2/3): Optimized Detection, Management and Treatment Modalities, Subsequent Management

1. Improving detection of histologic HSIL(CIN2/3) in the setting of primary HPV screening: When primary HPV screening is used, reflex cervical cytology (Pap) testing of all positive HPV tests (including HPV 16/18) is **preferred**. If reflex cervical cytology testing is not possible, direct referral for colposcopy is **acceptable**. If cervical cytology is not performed prior to the colposcopy, collection of a cervical cytology specimen at the colposcopy visit is **recommended**.

Rationale: Interim guidance for primary HPV screening recommends direct colposcopy referral without cervical cytology for HPV16/18+. However, this means that women at the highest risk of CIN3, those with HPV16+/HSIL would not have the option of expedited treatment. Combining a reflex cervical cytology result (specific test) with a positive HPV test (sensitive test) allows more precise, risk-based management of these patients.

2. Treatment guidance: General Population: For individuals with a diagnosis of histologic HSIL (CIN 2, CIN 3, or CIN 2,3) and colposcopy where the squamocolumnar junction is visualized, excision is **preferred** but ablation is **acceptable**, except in those that are pregnant, under age 25, or who desire future reproductive potential (see guideline below). A diagnostic excisional procedure is **recommended** for those with recurrent histologic HSIL (CIN 2, CIN 3, or CIN 2,3). Ablation is **unacceptable**, and a diagnostic excisional procedure is **recommended** for individuals with a histologic diagnosis of HSIL (CIN 2, CIN 3, or CIN 2,3) and colposcopy where the squamocolumnar junction is not fully visualized, or endocervical sampling showing HSIL (CIN 2, CIN 3, CIN 2,3), or CIN not graded. Hysterectomy is **unacceptable** as primary therapy for histologic HSIL (CIN 2, CIN 3, or CIN 2,3).

3. Treatment guidance: Individuals under age 25 or who desire future reproductive potential: For individuals under age 25 or those with desire for future reproductive potential, with a histologic diagnosis of HSIL (CIN2) specified, observation is **preferred** but treatment is **acceptable**; treatment is **recommended** if CIN 3 is specified. For a histologic diagnosis of HSIL (CIN 2/3) in those under age 25 or those desiring future reproductive potential, either treatment or observation for up to 24 months using cytology and colposcopy at 6 months intervals is **acceptable**, provided the squamocolumnar junction is fully visible and there is no HSIL in the endocervical sampling. If during surveillance cytology and colposcopy are both normal on two occasions, six months apart, subsequent surveillance should be a co-test 12 months after the last colposcopy. If histologic HSIL fails to resolve over a 2- year period, treatment is **recommended**.

Rationale: Observation of CIN2 (including CIN1/2, CIN2, and CIN2/3) was found to be safe in an observational cohort study of 2417 women aged 21-39, who were observed at 6 month intervals for a median of 48 months. Cancer

developed in six individuals (0.2%); 3 of these had follow up delays. 20% of participants met criteria to return to screening every 3 years and 50% remained in intensive surveillance. Other investigations of younger women, some of which also used less stringent criteria to define regression, have demonstrated a spontaneous CIN2 regression rate of 57-96% Observation of CIN2 is a reasonable option in those under age 25, who demonstrate high rates of resolution, and in older individuals desiring future reproductive potential. Patients should be advised that the risk of cancer is very low but not absent, and that the primary risk of observation of CIN2 is the need for prolonged intensive observation.

4. Treatment Modalities: Excisional therapy is the **preferred** therapy for treatment of patients diagnosed with or at high risk for HSIL(CIN2/3) in the United States. Ablation is **acceptable** after shared decision-making between the patient and a provider trained in ablative techniques, and consideration of risks and benefits. Nonsurgical therapies, including topical agents and therapeutic vaccines, currently remain investigational.

Rationale: Excision, including loop electrosurgical excision procedure (LEEP) and cervical conization, is the favored treatment modality for histologic HSIL(CIN2/3) in the United States, and the WHO recommends excisional therapy over ablative therapy when available. Unlike ablative techniques, excision provides a pathology specimen to evaluate for the presence of a higher grade of abnormality, including an occult invasive cancer that may have been missed on pre-treatment evaluation. Additionally, limited evidence indicates that excision results in an approximately 10% lower risk of persistent HSIL(CIN2/3) and HPV positivity than ablation, and is more than 50% more effective at reducing HSIL cytology at 6 months.

5. Initial surveillance following treatment: Following treatment for HSIL (CIN2+), HPV-based testing at 6 months is **preferred** regardless of margin status of the excisional specimen. In the setting of positive margins, repeat excision without interval cytology or HPV testing is **acceptable**, except in those under 25 years of age and those who desire future reproductive potential. Hysterectomy or continued observation with cytology and colposcopy at 6 months intervals is **acceptable** for patients whose excisional specimens have positive margins and for

whom a repeat excisional procedure is not feasible, or for those who have recurrent HSIL (CIN2+) and/or persistent HPV+ tests despite excisional treatment.

Rationale: The relative risk of persistent or recurrent HSIL (CIN2+) is almost 5-times higher following excisional treatment with positive margins compared to negative margins (RR 4.8, 95% CI 3.2-7.2; $p < 0.001$). Despite this significantly increased risk of persistent/recurrent dysplasia, the sensitivity of margin status to predict persistence/recurrence is low at only 55.8% (95% CI 45.8-65.5%); in a meta-analysis, only about half of individuals with persistent or recurrent HSIL (CIN2+) had positive margins at the time of their original excisional procedure. The low predictive ability of margin status for persistent/recurrent dysplasia argues against differentiating follow-up testing by margin status. In contrast, the sensitivity of HPV-based testing to predict persistent/recurrent HSIL (CIN2+) is 91.0% (95% CI 82.3-95.5%) at six months, and does not differ significantly between patients with positive versus negative margins.

The absolute risk of persistent/recurrent HSIL (CIN2+) following excision with positive margins is 17.1% (95% CI 12.7-22.1%), thus repeat excision without repeat testing is acceptable for certain patients after appropriate counseling and consideration of age and likelihood of subsequent resolution of dysplasia/HPV infection, desire for future reproductive potential, and ability to adhere to surveillance recommendations.

Hysterectomy is an option for patients in whom repeat excision is thought to be the best strategy after careful consideration of risks and benefits, but in whom a repeat excision is not feasible due to distortion of cervical anatomy from previous procedures, or for patients who have had persistent HSIL (CIN2+) and/or persistent HPV infection despite excisional treatments who want to minimize their future risk of dysplasia and reduce frequency of surveillance visits.

6. Long term surveillance following treatment: In patients treated for HSIL (CIN2/3), following the initial HPV-based test at six months, annual HPV-based testing is **preferred** until three consecutive negative tests have been obtained. Continued surveillance at 3-year intervals is recommended for at least 25 years following treatment of HSIL (CIN2/3) as well as AIS.³ When individuals with a history of treated HSIL(CIN2/3) or AIS reach the age of 65 years,

³ For management of vaginal cytology following HSIL, see Khan et al Gynecologic Oncology, 2016

continued surveillance at 3-year intervals is **acceptable** as long as they are in reasonably good health. Discontinuation of screening is **recommended** if they have a life-limiting condition. Management according to the highest grade abnormality found on histology, cytology, and/or HPV type (e.g. HPV 16/18+) is **recommended**.

Rationale: Both prospective longitudinal data and published literature indicate persistently elevated risk of developing recurrent CIN3+ and invasive cervical cancer following treatment for CIN3. While CIN2 may have lower risks, the inability to distinguish CIN2 from CIN3 in all cases, the use of two-tiered LAST terminology, and the desire for simplicity led to a single recommendation for follow-up.

Implications: Current recommendations for surveillance intervals are unclear. This recommendation clarifies that long-term surveillance at three years is recommended following treatment, and these patients do not ever qualify for screening at 5-year intervals.

GLOSSARY

Adenocarcinoma in Situ (AIS) AIS is a precursor of cervical adenocarcinoma; it is a rare but serious diagnosis. Treatment and subsequent management of AIS is outlined by the Society for Gynecologic Oncology.

The Bethesda system is a system for reporting cervical or vaginal cytologic diagnoses, used for reporting cervical cytology (Pap test) results. It was introduced in 1988 and revised in 1991, 2001, and 2014. The name comes from the location (*Bethesda*, Maryland) of the conference where this terminology was developed.

Cervical Intraepithelial Neoplasia (CIN) CIN is a pathologic diagnosis of squamous cervical abnormalities detected on histopathologic analysis of a cervical biopsy, endocervical curettage (ECC) or excisional biopsies such as cold knife cone or Loop Electrosurgical Excision Procedure (LEEP). CIN terminology is a 3-tiered system (CIN1, CIN2, CIN3) but a 2-tier system (LSIL/HSIL) is now recommended due to better reproducibility and correlation with HPV biology. Both systems are currently in use by pathology laboratories. CIN1 in the 3-tiered system corresponds to LSIL in the 2-tiered system. CIN2 (when supported by p16 immunohistochemistry) and CIN3 in the 3-tiered system both correspond to HSIL in the 2-tiered system. CIN3+, used as the endpoint for risk estimates in this document, includes CIN3, AIS, and cervical cancer.

Cervical cytology terms:

Negative for intraepithelial lesion or malignancy (NILM) *normal result*

Atypical Squamous Cells of Uncertain Significance (ASCUS) *minimally abnormal result*

Atypical Squamous Cells of Uncertain Significance cannot exclude high grade squamous intraepithelial lesion (SIL) (ASC-H) *has features of high grade SIL but not fully developed; considered as a high grade result in risk estimates*

Low grade Squamous Intraepithelial Lesion (LSIL) *minimally abnormal result that is the cytologic expression of HPV infection*

High Grade Squamous Intraepithelial Lesion (HSIL) *considered as a high grade result in risk estimates*

Atypical Glandular Cells (AGC) are managed *as a high grade result, AGC reporting is subclassified in Bethesda by cell type (glandular, endocervical, endometrial) and*

further stratified by risk as “favor neoplastic” (higher risk) or “not otherwise specified/NOS” for glandular and endocervical cell types.

HPV-based testing: this term is used in this document to describe the use of either co-testing or primary HPV screening for surveillance after abnormalities. It does not apply to reflex HPV testing in this document. *HPV testing, and positive HPV results discussed to throughout this document, refer to high-risk HPV types only.*

Loop Electrosurgical Excision Procedure (LEEP): procedure used to excise HSIL(CIN2/3) from the cervix. Also known as large loop excision of the transformation zone (LLETZ). Less invasive than other excisional procedures, usually performed in the outpatient setting.

Terminology used for recommendations:

Recommended: *Good data to support use when only one option is available*

Preferred: *Option is the best (or one of the best) when there are multiple options.*

Acceptable: *One of multiple options when there is either data indicating that another approach is superior or when there are no data to favor any single option.*

Not recommended: *Weak evidence against use and marginal risk for adverse consequences.*

Unacceptable: *Good evidence against use.*